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Bile acid profiles over 5 years following gastric bypass and duodenal switch – Results from a randomized clinical trial

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Bile acid profiles over 5 years following gastric bypass and duodenal switch – results from a randomized clinical trial

Manuscript type: Original Contribution

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Mini abstract: Bile acids have been suggested as possible key mediators of the metabolic effects after bariatric surgery. With 5-year follow-up data from a randomized clinical trial, we compare bile acid profile after gastric bypass and duodenal switch, and explore the relationship between bile acids and weight loss, lipid profile and glucose metabolism.

Short running head: Bile acid profile after bariatric surgery

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Author contributions

Conception or design: Kristinsson, Olbers, Mala

Acquisition, analysis or interpretation of the data: All authors

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Abstract

Background: Bile acids have been proposed as key mediators of the metabolic effects after bariatric surgery. Currently no reports on bile acid profiles after duodenal switch exist, and long-term data after gastric bypass are lacking.

Objective: To investigate bile acid profiles up to 5 years after Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch, and to explore the relationship between bile acids and weight loss, lipid profile and glucose metabolism.

Settings: Two Scandinavian University Hospitals.

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Methods: We present data from a randomized, clinical trial of 60 patients with body mass index 50–60 kg/m^2 operated with gastric bypass or duodenal switch. Repeated measurements of total and individual bile acids from fasting serum during 5 years after surgery were performed.

Results: Mean concentrations of total bile acids increased from 2.3 µmol/L (95% CI, -0.1 to 4.7) at baseline to 5.9 µmol/L (3.5 to 8.3) 5 years after gastric bypass and from 1.0 µmol/L (95% CI, -1.4 to 3.5) to 9.5 µmol/L (95% CI, 7.1 to 11.9) after duodenal switch, mean between-group difference was -4.8 µmol/L (95% CI, -9.3 to -0.3), P=.036. Mean concentrations of primary bile acids increased more after duodenal switch, while secondary bile acids increased proportionally across the groups. Higher levels of total bile acids at 5 years were associated with lower body mass index, greater weight loss and lower total cholesterol.

Conclusions: Total bile acid concentrations increased substantially over 5 years after both gastric bypass and duodenal switch, with greater increases in total and primary bile acids after duodenal switch.

Keywords: Bariatric surgery; metabolic surgery; Roux-en-Y gastric bypass; gastric bypass, biliopancreatic diversion with duodenal switch; duodenal switch; randomized controlled trial; randomized clinical trial; bile acids, bile acid profiles

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Introduction

Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch (BPD/DS) provide considerable and durable weight loss and improve obesity-related diseases such as type 2 diabetes [1,2]. BPD/DS is more effective than RYGB to induce weight loss, improve glycemic control and lipid profiles [3-5]. The mechanisms of action for weight loss and metabolic improvements are complex and remain largely unknown.

Bile acids (BAs) participate in the control of glucose and lipid metabolism and energy homeostasis [6-8]. They act as signaling hormones by activating nuclear receptors and membrane coupled receptors in the intestine, liver, muscle and adipose tissue. Furthermore, they regulate the balance of different species of the microbiome, and the microbiome interacts reciprocally with the metabolism and composition of BAs [8,9]. BAs have been suggested as important mediators of weight loss and metabolic changes after bariatric surgery [10-13], and different fractions of BAs have been linked to different features of glucose metabolism [14,15]. Most studies report increased BA concentrations after RYGB [16,17], but studies exploring changes in BA fractions are inconsistent [18-20]. There are, to our knowledge, no reports of changes in BA profiles after BPD/DS, and there are no reports on BA profiles long term after bariatric surgery.

We used data from a randomized clinical trial to explore the effects of RYGB and BPD/DS on BA concentrations. We aimed to investigate the long term effect of the two procedures on total BA

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concentrations and fractions, and to explore the relationship between BAs and measures of weight loss, blood lipids and glucose metabolism.

Methods

Study design

The rationale and design of our randomized clinical trial conducted at two Scandinavian University Hospitals has been reported previously [21]. Shortly, patients aged 20-50 years with body mass index (BMI, calculated as weight divided by height in meters squared) of 50-60 seeking bariatric surgery were randomized to receive RYGB or BPD/DS. The regional ethics committees approved the protocol, and all patients provided written consent. The trial was registered at clinicaltrials.gov Identifier NCT00327912.

The procedures were performed laparoscopically with standardized methodology [21]. In RYGB the alimentary limb was 150 cm and the biliopancreatic limb was 50 cm. In BPD/DS, the alimentary limb was 200 cm and the common channel was 100 cm. All patients with the gallbladder in situ were recommended daily oral intake of ursodeoxycholic acid (500 mg) for 6 months postoperatively as gall stone prophylaxis.

Results on weight loss, cardio-metabolic risk factors, nutritional status, adverse events, and patient-reported outcome measures have been reported previously [5,21-24]. The present report implements data from baseline, 1, 2 and 5 years.

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Blood sample collection, laboratory analysis and calculations

Venous blood samples were obtained after an overnight fast at each study visit. Samples clotted 30 minutes at room temperature and serum was separated with centrifugation (1700 x g, 10 min) and aliquots were stored at -70°C in a biobank for later analyses.

Serum BA profile were analyzed with high performance liquid chromatography (Jasco^{TM}, USA) coupled to tandem mass spectrometry (Applied Biosystems, Cheshire, UK), in the Department of Clinical Biochemistry at the King's College Hospital NHS Foundation Trust in London, using established modifications of a previously described method [25]. The BAs quantified included 15 fractions. For individual BAs with values below the lowest area of detection we used a computer based method with imputation of a random value between 0 and the lowest area of detection. Composite concentrations of BAs were calculated by summing concentrations of individual BAs.

Statistics

The sample size was calculated for the primary end point of the study which was change in BMI between groups [21]. Because of the explorative nature of this substudy no power calculations were performed for the measures in this study. We used linear mixed model analyses to estimate mean changes in total and composite values of BA concentrations over time. The linear mixed models included fixed effects for procedure, time, and procedure x time interaction. Time was modelled as piecewise linear with two knots (1 and 2 years after surgery). A random intercept was used. Since cholecystectomy may influence BA concentrations and more patients

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with BPD/DS had cholecystectomy, we performed sensitivity analyses on total BAs with samples obtained after cholecystectomy excluded. We also compared the composition of individual BAs and composite values between patients with and without cholecystectomy, and revealed a comparable pattern between the groups. Hence we decided to include all patients in the descriptive analyses.

For between group changes of individual BAs, we used linear regression with BA concentrations at 5 years as dependent variable and the baseline measurement and surgical procedure as independent variables. Although the distribution of the BA concentrations was slightly skewed, we found the difference in means to be a suitable effect measure, and that the distribution of the residuals from the linear regression models did not deviate much from the normal distribution.

To explore the relationship between total BA concentrations and measures of weight loss, lipid and glucose metabolism we used Spearman's rank order coefficient. A two-tailed $P < .05$ was considered statistically significant. Data were analyzed with Stata 14 College Station, TX (StataCorp LP) and IBM SPSS Statistics for Windows, version 24, Armonk, NY (IBM Corporation).

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Results

Patient characteristics are described in Table 1. Before surgery, 18% of the patients had type 2 diabetes, and all of these patients experienced partial or complete remission 5 years after surgery. At 1, 2 and 5 years, 1 (1.7%), 2 (3.3%) and 5 (8.3%) of the patients were lost to follow-up, respectively. Five patients (3 RYGB and 2 BPD/DS) had cholecystectomy before study inclusion. Additional 6 patients (1 RYGB and 5 BPD/DS) had cholecystectomy during the study. As previously reported, patients with BPD/DS had substantially greater BMI and weight loss compared to RYGB patients, corresponding to a difference of 24.9 kg or 8.5 kg/m^2 between groups[5].

Total and composite values of BAs are presented in Table 2 and show that total bile acid concentrations increased significantly more after BPD/DS compared to RYGB. We observed large intra- and inter-variability of total BAs after both procedures, and the variability tended to increase after surgery (Figure 1).

At 5 years, patients with cholecystectomy had higher concentrations of total BAs than patients without cholecystectomy; mean 19.7 µmol/L (10.6 to 28.8) vs 4.6 µmol/L (95% CI, 3.2 to 5.9), P<.001 (Figure 1). We therefore did sensitivity analysis with only patients with the gall bladder in situ included (Table 2).

The concentrations of individual BAs are shown in Table 3. The larger increase in total BA concentrations after BPD/DS compared to RYGB was primarily driven by greater increases in

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primary BAs, predominantly the unconjugated primary BAs cholic and chenodeoxycholic acid and their glycine-conjugates (Table 2 and 3). The concentrations of secondary BAs increased after surgery in both groups, with no between-group difference. The composition of BAs changed differently, with an increase in the proportion of primary BAs after BPD/DS and an increase in the proportion of secondary BAs after RYGB (Table 1).

The ratio of the 12α-hydroxylated / non-12α-hydroxylated BAs increased from 0.8 (95% CI, 0.6 to 1.0) at baseline to 1.1 (95% CI, 0.9 to 1.3) 5 years after RYGB (P=.04) and from 0.7 (95% CI, 0.6 to 0.9) to 1.3 (1.0 to 1.5) after BPD/DS (P<.001). Mean between group difference was 0.2 (95% CI, -0.1 to 0.5); P=.21.

At 5 years, higher levels of fasting total BA concentrations were associated with lower BMI and measures of weight loss (Table 4). We also observed an inverse correlation between total BAs and total cholesterol. Changes in total levels of BA concentrations between baseline and 5 years correlated significantly with weight loss.

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Discussion

In this study of BA profiles during 5 years of RYGB and BPD/DS, we observed substantial increase in the fasting serum concentrations after both procedures, with greater increase in total BA concentrations after BPD/DS compared to RYGB. The composition of BAs changed differently across the groups.

Several other studies have investigated BA concentrations after RYGB. Most short-term studies (< 2 months after surgery) report unchanged or decreased levels of total BAs [26-28], while most studies reporting data from several months and years after surgery report increased concentrations [18,20,29-32]. Our findings are in accordance with the existent literature, and extend the current knowledge by showing that the BA levels apparently continue to increase up to 5 years after RYGB. Changes in BAs after BPD/DS have not previously been explored. Interestingly, in a model of duodenal-jejunal bypass with short and long biliopancreatic limbs, increased BA concentrations were observed in rats with long biliopancreatic limb, together with suppression of weight gain and improved glucose metabolism [33]. This experimental study supports that a long biliopancreatic limb may be important for the metabolic improvements after bariatric surgery and suggests that BAs play a role, but the causal relationship between BAs and the metabolic improvements is still uncertain.

The mechanisms for the higher BA concentrations after BPD/DS compared to RYGB are unknown, and can arise through several mechanisms. Differences in intestinal absorption may contribute. The longer biliopancreatic limb in BPD/DS leads to transportation of high

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concentrations of primary BAs through a longer segment of the small bowel before they mix with food and promote fat digestion and absorption in the common channel, and could therefore be more available for absorption. We found that the higher concentrations of primary BAs after BPD/DS were predominantly due to increases in the unconjugated and glycine-conjugated primary BAs. In normal anatomy, BAs in the upper intestine are dominated by primary conjugated BAs [34]. One possible explanation for the rise in unconjugated BAs could be that microbial contamination of the small intestine due to altered gut anatomy causes bacterial deconjugation of BAs and subsequently absorption in the biliopancreatic limb [34-36]. This could mean that the great elevation of BAs that we observe after BPD/DS (and also RYGB) not necessarily reflects an actual increase in the size of the bile salt pool, but could rather be a result of shorter enterohepatic cycling.

The repeated measurements in our study revealed that BAs continued to increase years after surgery. Changed microbial metabolism may be involved as they can modulate the BA pool [37]. Changes in BA synthesis or excretion could also be involved [38]. Cholesterol is an essential constituent of BAs. Our finding of an inverse correlation between total BAs and total cholesterol, together with a greater reduction in total cholesterol, LDL cholesterol and triglycerides after BPD/DS compared to RYGB in the main study, leads us to speculate that increased hepatic production and/or increased fecal excretion of BAs contribute to our observations.

We found significantly higher serum BA levels in patients with cholecystectomy compared to patients with the gall bladder in situ 5 years after surgery. This may, completely or partly, be

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attributable to increased cycling of the BA pool in the enterohepatic circulation due to lack of storage capacity [39,40].

We observed a relationship between higher total BA concentrations at 5 years and lower BMI, greater weight loss and lower serum total cholesterol. These observations must be considered as explorative and no conclusions about a causal relationship between these variables and bile acid concentrations can be done. As in several other studies, we were not able to demonstrate any correlation between BAs and markers of glucose metabolism and insulin resistance [18,20,27,28]. We found large variations in fasting BA concentrations both within and between individuals, as depicted in Figure 1. This is in line with studies of non-bariatric subjects, which found large diurnal variations within individuals [41,42] and large variations in production and concentrations between individuals [43,44].

Insulin regulates BA composition, in part by regulating the BA 12-α hydroxylase (CYP8B1), and it has been shown that a high ratio of 12α-hydroxylated / non-12α-hydroxylated BAs is associated with more insulin resistance [14]. A study of patients with type 2 diabetes observed, contrary to their hypothesis, an increase in this ratio after RYGB [28]. Our study, which mostly included non-diabetic subjects, also demonstrated an increased ratio after both procedures at 5 years.

Strengths of this study include the randomized design with a well-defined patient population, close to complete follow-up up at all time points, and standardized surgical procedures. BA composition was carefully characterized at several time points and includes long-term

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evaluation. Limitations include measurements of BAs in peripheral blood. We did not measure post-prandial BA responses, markers of production, fecal excretion, enteric hormones or fecal microbiome, which would have helped us to better understand the physiological changes that underlie our findings. The findings of this study may not generalize to patients outside the BMI and age restriction in our study, and probably of more importance, to patients with type 2 diabetes or severe metabolic disease. Previous studies have shown different bile acid profiles and responses in subjects with type 2 diabetes compared to non-diabetic subjects both before and after bariatric surgery [11,45].

We have demonstrated larger increases in serum BAs and a different change in bile acid species and composition after BPD/DS than after RYGB. Whether there is a causal relationship between the higher increase in BAs after BPD/DS and the superior metabolic effects compared to RYGB remains unknown. Our findings of a relationship between BAs and measures of weight and weight loss and total cholesterol may suggest that BAs play a role in the metabolic improvements after the two procedures, but a causal relationship is still unknown. Other mechanisms are involved, and isolating the effect of changes in the enterohepatic circulations of BAs has not been achieved. Further mechanistic studies are warranted to reveal the physiology of altered BA concentrations after bariatric surgery, and to investigate the possible impact of BAs on the metabolic improvements. Measures from patients with normal gut anatomy have shown large variability in the BA concentrations within and between individuals, and our study implicates that this variability fluctuates even more after RYGB and BPD/DS. This, and the fact

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that cholecystectomy may result in a substantial change in the enterohepatic circulation, should be taken into account in the planning of future studies.

Conclusions

Fasting serum concentrations of total BAs increased substantially over 5 years after both RYGB and BPD/DS. Patients undergoing BPD/DS had greater increase in total and primary BAs in comparison to RYGB. At 5 years, there was a positive correlation between total BA concentration and weight loss, and an inverse correlation between total BA concentrations and BMI and total cholesterol.

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Table 1. Baseline and 5-year data by treatment group

Variable	RYGB (n=31)	BPD/DS (n=29)
Age at inclusion, years	35.2 (7.0)	36.1 (5.3)
Female, n (%)	23 (74.2)	19 (65.5)
White, n (%)	30 (96.8)	27 (93.1)
Body weight, kg		
Baseline	162.1 (24.1)	162.2 (19.7)
5 y change from baseline	-42.8 (21.6)	-66.5 (23.3)
BMI (kg/m^2)		
Baseline	54.8 (3.2)	55.2 (3.5)
5 y change from baseline	-13.1 (7.3)	-20.4 (7.1)
Total cholesterol, mg/dL		
Baseline	186 (34)	186 (26)
5 y change from baseline	-7 (29)	-53 (23)
LDL-C, mg/dL		
Baseline	110 (25)	110 (24)
5 y change from baseline	-10 (25)	-40 (24)
HDL-C, mg/dL		
Baseline	46 (10)	45 (10)
5 y change from baseline	17 (12)	7 (10)
Triglycerides, mg/dL		
Baseline	147 (75)	160 (59)
5 y change from baseline	-62 (61)	-86 (51)
Glucose, mg/dL		
Baseline	110 (31)	114 (38)
5 y change from baseline	-10 (28)	-27 (42)
Cholecystectomy, n (%)		
Baseline	3 (9.7)	2 (6.9)
5 y	4 (12.9)	7 (24.1)
Type 2 diabetes, n (%)		
Baseline	5 (16.1)	6 (20.7)
5 y	0	0
Use of glucose-lowering medication, n (%)		
Baseline	3 (9.7)	2 (6.9)
5 y	0	0
Hypertension, n (%)		
Baseline	8 (25.8)	8 (27.6)
5 y	4 (14.8)	7 (25.0)
Metabolic syndrome, n (%)		
Baseline	20 (64.5)	23 (79.3)
5 y	3 (11.1)	1 (3.6)

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Abbreviations: RYGB, Roux-en-Y gastric bypass; BPD/DS, biliopancreatic diversion with duodenal switch; y, years; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
Mean (SD) are reported for continuous variables.

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Table 2. Composite measures of bile acid concentrations after RYGB and BPD/DS up to 5 years after surgery

Bile acids		Mean concentrations (95% CI)	Mean change (5y–B) within group (95% CI); P value	Mean change between groups (5y–B); P value
Total, μmol/L				
Preop	RYGB	2.3 (-0.1, 4.7)	3.6 (0.5, 6.8); P=.025	-4.8 (-9.3, -0.3); P=.036
	BPD/DS	1.0 (-1.4, 3.5)	8.5 (5.3, 11.6); P<.001	
1 y	RYGB	2.5 (0.1, 5.0		
	BPD/DS	6.4 (3.9, 9.0)		
2 y	RYGB	4.7 (2.3, 7.1)		
	BPD/DS	8.2 (5.6, 10.8)		
5 y	RYGB	5.9 (3.5, 8.3)		
	BPD/DS	9.5 (7.1, 11.9)		
Glycine conjugated, μmol/L				
Preop	RYGB	1.2 (-0.3, 2.7)	1.7 (-0.2, 3.7); P=.08	-2.4 (-5.2, 0.3); P=.09
	BPD/DS	0.6 (-1.0, 2.1)	4.2 (2.2, 6.1); P<.001	
1 y	RYGB	1.2 (-0.3, 2.8)		
	BPD/DS	2.8 (1.2, 4.4)		
2 y	RYGB	1.7 (0.2, 3.1)		
	BPD/DS	3.5 (1.9, 5.1)		
5 y	RYGB	3.0 (1.5, 4.5)		
	BPD/DS	4.7 (3.3, 6.2)		
Taurine conjugated, μmol/L				
Preop	RYGB	0.14 (0.02, 0.27)	0.2 (0.009, 0.3); P=.37	0.1 (-0.1, 0.3); P=.50
	BPD/DS	0.001 (-0.12, 0.13)	0.1 (-0.1, 0.2); P=.26	
1 y	RYGB	0.1 (-0.008, 0.2)		
	BPD/DS	0.1 (-0.02, 0.2)		
2 y	RYGB	0.1 (-0.004, 0.2)		
	BPD/DS	0.1 (-0.01, 0.3)		
5 y	RYGB	0.2 (0.009, 0.3)		
	BPD/DS	0.1 (-0.1, 0.2)		
Total unconjugated, μmol/L				
Preop	RYGB	0.9 (-0.6, 2.5)	1.7 (-0.3, 3.7); P=.09	-2.5 (-5.3, 0.3); P=.09

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	BPD/DS	0.5 (-1.1, 2.0)	4.2 (2.2, 6.2); P<.001	
1 y	RYGB	1.2 (-0.4, 2.7)		
	BPD/DS	3.5 (1.9, 5.1)		
2 y	RYGB	2.9 (1.4, 4.4)		
	BPD/DS	4.6 (3.0, 6.3)		
5 y	RYGB	2.7 (1.2, 4.2)		
	BPD/DS	4.7 (3.2, 6.2)		
Proportion Conjugated, %				
Preop	RYGB	64.8 (54.0, 75.5)	-12.9 (-26.9, 1.0); P=.07	6.9 (-12.7, 26.5);P=.49
	BPD/DS	54.9 (44.0, 65.8)	-19.8 (-33.6, -6.0); P=.005	
1 y	RYGB	54.3 (43.5, 65.0)		
	BPD/DS	47.3 (36.3, 58.2)		
2 y	RYGB	57.5 (47.1, 67.9)		
	BPD/DS	42.2 (31.1, 53.4)		
5 y	RYGB	51.8 (41.3, 62.3)		
	BPD/DS	35.1 (24.9, 45.3)		
Proportion unconjugated, %				
Preop	RYGB	35.2 (24.5, 46.0)	12.9 (-1.0, 26.9); P=.07	-6.9 (-26.5, 12.7); P=.49
	BPD/DS	45.1 (34.2, 56.0)	19.8 (6.0, 33.6); P=.005	
1 y	RYGB	45.7 (35.0, 56.5)		
	BPD/DS	52.7 (41.8, 63.7)		
2 y	RYGB	42.5 (32.1, 52.9)		
	BPD/DS	57.8 (46.6, 68.9)		
5 y	RYGB	48.2 (37.7, 58.7)		
	BPD/DS	64.9 (54.7, 75.1)		
Primary, µmol/L				
Preop	RYGB	1.6 (-0.3, 3.4)	2.4 (-0.1, 4.8); P=.06	-4.3 (-7.8, -0.9); P=.015
	BPD/DS	0.7 (-1.2, 2.6)	6.7 (4.2, 9.1); P<.001	

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1 y	RYGB	1.7 (-0.2, 3.6)		
	BPD/DS	4.9 (3.0, 6.9)		
2 y	RYGB	3.4 (1.6, 5.2)		
	BPD/DS	5.8 (3.8, 7.8)		
5 y	RYGB	4.0 (2.1, 5.8)		
	BPD/DS	7.4 (5.6, 9.2)		
Secondary, μmol/L				
Preop	RYGB	0.7 (-0.03, 1.4)	1.3 (0.3, 2.2); P=.01	-0.5 (-1.9, 0.9); P=.47
	BPD/DS	0.4 (-0.4, 1.1)	1.8 (0.8, 2.7); P<.001	
1 y	RYGB	0.8 (0.1, 1.6)		
	BPD/DS	1.5 (0.7, 2.3)		
2 y	RYGB	1.3 (0.5, 2.0)		
	BPD/DS	2.4 (1.6, 3.2)		
5 y	RYGB	2.0 (1.2, 2.7)		
	BPD/DS	2.1 (1.4, 2.9)		
Proportion Primary, %				
Preop	RYGB	69.0 (61.7, 76.3)	-12.2 (-21.7, -2.6); P=.012	-28.4 (-41.8, -15.0); P<.001
	BPD/DS	56.9 (49.5, 64.3)	16.3 (6.9, 25.7); P<.001	
1 y	RYGB	62.5 (55.2, 69.8)		
	BPD/DS	69.3 (61.8, 76.8)		
2 y	RYGB	64.6 (57.5, 71.7)		
	BPD/DS	75.2 (67.6, 82.8)		
5 y	RYGB	56.9 (50.0, 64.0)		
	BPD/DS	73.2 (66.2, 80.1)		
Proportion secondary, %				
Preop	RYGB	31.0 (23.7, 38.3)	12.2 (2.6, 21.7); P=.012	28.4 (15.0, 41.8); P<.001
	BPD/DS	43.1 (35.7, 50.4)	-16.3 (-25.7, -6.9); P<.001	
1 y	RYGB	37.5 (30.2, 44.8)		
	BPD/DS	30.7 (23.2, 38.2)		
2 y	RYGB	35.4 (28.3, 42.5)		
	BPD/DS	24.8 (17.2,		

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		32.4)		
5 y	RYGB	43.1 (36.0, 50.3)		
	BPD/DS	26.8 (19.9, 33.8)		
Total, cholecystectomy excluded[a]				
Preop	RYGB	2.1 (0.3, 3.9)	1.4 (-1.0, 3.7); P=.26	-3.4 (-6.8, -0.4); P=.048
	BPD/DS	1.1 (-0.8, 2.9)	4.8 (2.4, 7.2); P<.001	
1 y	RYGB	2.5 (0.7, 4.3)		
	BPD/DS	6.1 (4.2, 8.0)		
2 y	RYGB	3.7 (1.9, 5.5)		
	BPD/DS	6.5 (4.6, 8.5)		
5 y	RYGB	3.5 (1.6, 5.3)		
	BPD/DS	5.9 (4.0, 7.8)		

Abbreviations: RYGB, Roux-en-Y gastric bypass; BPD/DS, biliopancreatic diversion with duodenal switch; Preop, preoperatively.
[a]Sensitivity analyses with bile acid concentration measures obtained after patients with cholecystectomy (n=11) excluded.

Table 3. Individual bile acid concentrations and fractions before and 5 years after RYGB and BPD/DS

	Procedure	**Preop**	**5 y**	**Mean between-group change[a]**	**P value[a]**
Primary unconjugated bile acids					
CA µmol/L, mean (95% CI)	RYGB	0.22 (0.07, 0.39)	0.70 (-0.13, 1.53)	0.84 (-0.36, 2.04)	.16
	BPD/DS	0.06 (0.03, 0.09)	1.63 (0.82, 2.46)		
% TBA, mean (95% CI)	RYGB	7.1 (3.7, 10.4)	8.0 (4.0, 12.1)	10.2 (2.9, 17.4)	.007
	BPD/DS	4.0 (2.3, 5.6)	18.7 (12.8, 24.6)		

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CDCA µmol/L, mean (95% CI)	RYGB	0.26 (0.11, 0.40)	1.03 (-0.19, 2.25)	0.18 (-1.17, 1.52)	.79
	BPD/DS	0.12 (0.07, 0.17)	1.37 (0.85, 1.89)		
% TBA, mean (95% CI)	RYGB	9.1 (5.7, 12.6)	10.3 (5.0, 15.7)	7.1 (0.4, 13,9)	.039
	BPD/DS	7.9 (5.4, 10.4)	17.6 (13.3, 21.9)		
Primary conjugated bile acids					
GCA µmol/L, mean (95% CI)	RYGB	0.19 (0.11, 0.28)	0.32 (0.17, 0.47)	0.91 (-0.02, 1.83)	.05
	BPD/DS	0.12 (0.08, 0.16)	1.26 (0.36, 2.16)		
% TBA, mean (95% CI)	RYGB	7.9 (5.7, 10.1)	7.6 (5.4, 9.7)	0.7 (-3.0, 4.5)	.69
	BPD/DS	7.3 (5.7, 8.9)	8.3 (5.1, 11.4)		
TCA µmol/L, mean (95% CI))	RYGB	0.04 (0.01, 0.07)	0.05 (0.03, 0.07)	0.001 (-0.03, 0.03)	.93
	BPD/DS	0.03 (0.02, 0.03)	0.05 (0.02, 0.07)		
% TBA, mean (95% CI)	RYGB	1.4 (0.7, 2.1)	2.2 (1.1, 3.3)	-0.02 (-0.04, 0.01)	.28
	BPD/DS	2.0 (1.5, 5.6)	0.8 (0.4, 1.2)		
GCDCA µmol/L, mean (95% CI))	RYGB	0.65 (0.44, 0.85)	1.04 (0.59, 1.50)	1.49 (-0.57, 3.04)	.15
	BPD/DS	0.39 (0.27, 0.51)	2.73 (0.79, 4.67)		
% TBA, mean (95% CI)	RYGB	28.2 (24.2, 32.2)	24.1 (18.0, 30.1)	-7.4 (-15.8, 1.0)	.08

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	BPD/DS	24.1 (19.7, 28.5)	19.3 (12.3, 26.2)		
TCDC					
µmol/L, mean (95% CI)	RYGB	0.06 (0.03, 0.09)	0.10 (0.05, 0.14)		
	BPD/DS	0.04 (0.03, 0.05)	0.07 (0.04, 0.10)		
% TBA, mean (95% CI)	RYGB	3.0 (2.1, 3.9)	2.8 (1.6, 4.1)	-1.7 (-3.0, -0.5)	.009
	BPD/DS	2.8 (1.9, 3.7)	1.1 (0.6, 1.6)		
Secondary unconjugated bile acids					
DCA					
µmol/L, mean (95% CI)	RYGB	0.3 (0.1, 0.4)	0.8 (0.3, 1.3)	0.12 (-0.43, 0.66)	.67
	BPD/DS	0.2 (0.2, 0.3)	0.9 (0.6, 1.2)		
% TBA, mean (95% CI)	RYGB	11.3 (7.8, 14.8)	16.0 (12.5, 19.4)	-1.3 (-7.7, 5.1)	.68
	BPD/DS	14.8 (11.5, 18.1)	15.5 (10.0, 20.9)		
UDCA					
µmol/L, mean (95% CI)	RYGB	0.06 (0.04, 0.08)	0.09 (0.01, 0.17)	0.02 (-0.07, 0.10)	.74
	BPD/DS	0.05 (0.03, 0.06)	0.10 (0.06, 0.14)		
% TBA, mean (95% CI)	RYGB	3.2 (2.3, 4.1)	1.8 (1.2, 2.3)	0.3 (-0.7, 1.3)	.55
	BPD/DS	3.1 (2.3, 4.0)	2.1 (1.1, 3.0)		
LCA					
µmol/L, mean (95% CI)	RYGB	0.07 (0.06, 0.09)	0.07 (0.06, 0.09)	0.01 (-0.02, 0.31)	.51
	BPD/DS	0.07 (0.05, 0.09)	0.08 (0.07, 0.10)		
% TBA, mean	RYGB	4.5 (2.9, 6.1)	3.8 (2.0,	-1.9 (-4.0,	.08

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(95% CI)			5.6)	0.2)	
	BPD/DS	5.6 (3.6, 7.6)	2.0 (0.8, 3.2)		
Secondary conjugated bile acids					
GDCA					
µmol/L, mean (95% CI)	RYGB	0.2 (0.1, 0.3)	0.5 (0.3, 0.6)	0.34 (-0.38, 1.05)	.34
	BPD/DS	0.1 (0.1, 0.2)	0.8 (0.1, 1.5)		
% TBA, mean (95% CI)	RYGB	8.5 (6.5, 10.4)	11.9 (9.1, 14.7)	-5.2 (-8.7, -1.7)	.005
	BPD/DS	8.1 (5.8, 10.5)	6.7 (4.5, 9.0)		
TDCA					
µmol/L, mean (95% CI)	RYGB	0.04 (0.03, 0.05)	0.07 (0.04, 0.09)	-0.02 (-0.05, 0.01)	.28
	BPD/DS	0.02 (0.02, 0.03)	0.04 (0.02, 0.06)		
% TBA, mean (95% CI)	RYGB	2.5 (1.5, 3.5)	2.2 (1.5, 2.9)	-1.4 (-2.2, -0.6)	.001
	BPD/DS	1.8 (1.1, 2.4)	0.7 (0.3, 1.1)		
GUDCA					
µmol/L, mean (95% CI)	RYGB	0.10 (0.07, 0.14)	0.09 (0.03, 0.15)	0.09 (-0.04, 0.2)	.18
	BPD/DS	0.07 (0.05, 0.09)	0.18 (0.07, 0.29)		
% TBA, mean (95% CI)	RYGB	4.9 (3.8, 5.9)	2.2 (1.4, 3.1)	-0.1 (-1.2,0.9)	.82
	BPD/DS	4.5 (3.5, 5.6)	2.2 (1.4, 2.9)		
TUDCA					
µmol/L, mean (95% CI)	RYGB	0.02 (0.01, 0.02)	0.02 (0.02, 0.02)	-0.001 (-0.006, 0.005)	.78
	BPD/DS	0.02 (0.02, 0.02)	0.02 (0.02, 0.02)		
% TBA, mean (95% CI)	RYGB	1.1 (0.7, 1.5)	1.0 (0.5, 1.5)	-0.6 (-1.1, 0.002)	.05
	BPD/DS	1.5 (1.1, 1.8)	0.4 (0.2,		

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			0.7)		
GLCA					
µmol/L, mean (95% CI)	RYGB	0.06 (0.04, 0.08)	0.08 (0.06, 0.10)		
	BPD/DS	0.09 (0.07, 0.11)	0.09 (0.07, 0.11)		
% TBA, mean (95% CI)	RYGB	3.3 (1.9, 4.7)	3.4 (1.8, 4.9)	-1.2 (-3.4, 1.0)	.28
	BPD/DS	6.7 (5.0, 8.3)	2.2 (0.9, 3.5)		
TLCA					
µmol/L, mean (95% CI)	RYGB	0.07 (0.05, 0.10)	0.06 (0.04, 0.08)		
	BPD/DS	0.08 (0.06, 0.10)	0.09 (0.07, 0.11)		
% TBA, mean (95% CI)	RYGB	4.2 (2.4, 6.0)	2.7 (1.5, 3.8)	0.1 (-1.8, 2.0)	.92
	BPD/DS	5.9 (3.9, 7.8)	2.5 (1.0, 4.0)		

Abbreviations: RYGB, Roux-en-Y gastric bypass; BPD/DS, biliopancreatic diversion with duodenal switch; Preop, preoperatively; TBA, total bile acids; CA, cholic acid; CDCA, chenodeoxycholic acid; GCA, glycocholic acid; TCA, taurocholic acid; GCDCA, glycochenodeoxycholic acid; TCDC, taurochenodeoxycholic acid; DCA, deoxycholic acid; UDCA, ursodeoxycholic acid; LCA, lithocholic acid; GDCA, glycodeoxycholic acid; TDCA, taurodeoxycholic acid; GUDCA, glycoursodeoxycholic acid; TUDCA, tauroursodeoxycholic acid; GLCA, glycolithocholic acid; TLCA, taurolithocholic acid.

[a]From multiple regression with the 5 y value as dependent variable and procedure and preoperative value as independent variable.

The lowest area of detection for the individual bile acids: 0.05 µmol/L (TUDCA), 0.06 µmol/L (GUDCA), 0.07 µmol/L (CDCA, TCA, TCDCA, UDCA, TDCA), 0.08 µmol/L (DCA), 0.10 µmol/L (GCA) 0.14 (GDCA), 0.16 µmol/L (GCDCA, LCA), 0.17 µmol/L (GLCA, TLCA). Random imputation (between 0 and lowest area of detection) was used for measurements below the lowest area of detection.

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Table 4. Correlation analyses of fasting serum concentrations of total bile acids and BMI, fasting serum lipids and measures of glucose metabolism at 5 years

	Spearman's Rho[a]	95% CI	P value
5y measurements	**Total bile acid concentrations** (n=43)		
Body mass index (kg/m^2)	-0.31	-0.56, -0.01	.042
Body mass index change (5y–B)	-0.35	-0.59, -0.06	.023
Body weight, kg	-0.26	-0.52, 0.04	.09
Body weight change (5y–B), kg	-0.39	-0.62, -0.10	.010
Body weight change (5y–B), %	-0.35	-0.56, -0.06	.021
Total cholesterol, mg/dL	-0.33	-0.57, -0.03	.036
LDL-C, mg/dL	-0.28	-0.54, 0.02	.08
HDL-C, mg/dL	-0.09	-0.39, 0.21	.56
Triglycerides, mg/dL	-0.20	-0.47, 0.11	.21
Glucose, mg/dL	-0.17	-0.45, 0.14	.28
HbA1c, %	-0.12	-0.41, 0.19	.46
C-peptide, ng/mL	-0.19	-0.46, 0.12	.24
Insulin, µIU/mL	-0.30	-0.55, 0.00	.05
Proinsulin / insulin ratio	0.01	-0.38, 0.39	.93
HOMA-IR	-0.29	-0.54, 0.01	.06
Change from baseline to 5y[b]	**Change in total bile acid Concentrations**[b] (n=39)		
Body mass index (kg/m^2)	-0.30	-0.56, 0.02	.06
Body weight (kg)	-0.35	-0.60, -0.04	.041
Body weight (%)	-0.31	-0.57, 0.01	.06
Total cholesterol, mg/dL	-0.29	-0.55, 0.03	.08
LDL-C,	-0.31	-0.57, 0.01	.06
HDL-C, mg/dL	-0.06	-0.37, 0.26	.73
Triglycerides, mg/dL	0.05	-0.36, 0.27	.77
Glucose, mg/dL	0.03	-0.30, 0.34	.87
C-peptide, ng/mL	0.09	-0.23, 0.39	.59
Insulin, µIU/mL	0.27	-0.03, 0.53	.12
Proinsulin / insulin ratio	0.14	-0.18, 0.44	.43
HOMA-IR	0.22	-0.10, 0.50	.21

Abbreviations: BMI, body mass index; LDL-cholsterol, low-density lipoprotein cholesterol; HDL-cholesterol, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin A1c, HOMA-IR, homeostatic model assessment - insulin resistance.

Correlation analyses were performed with both surgical groups combined and with values after cholecystectomy excluded.

[a]11 patients with cholecystectomy at 5 years were excluded from all correlation analyses.

[b]5y minus baseline measurements.

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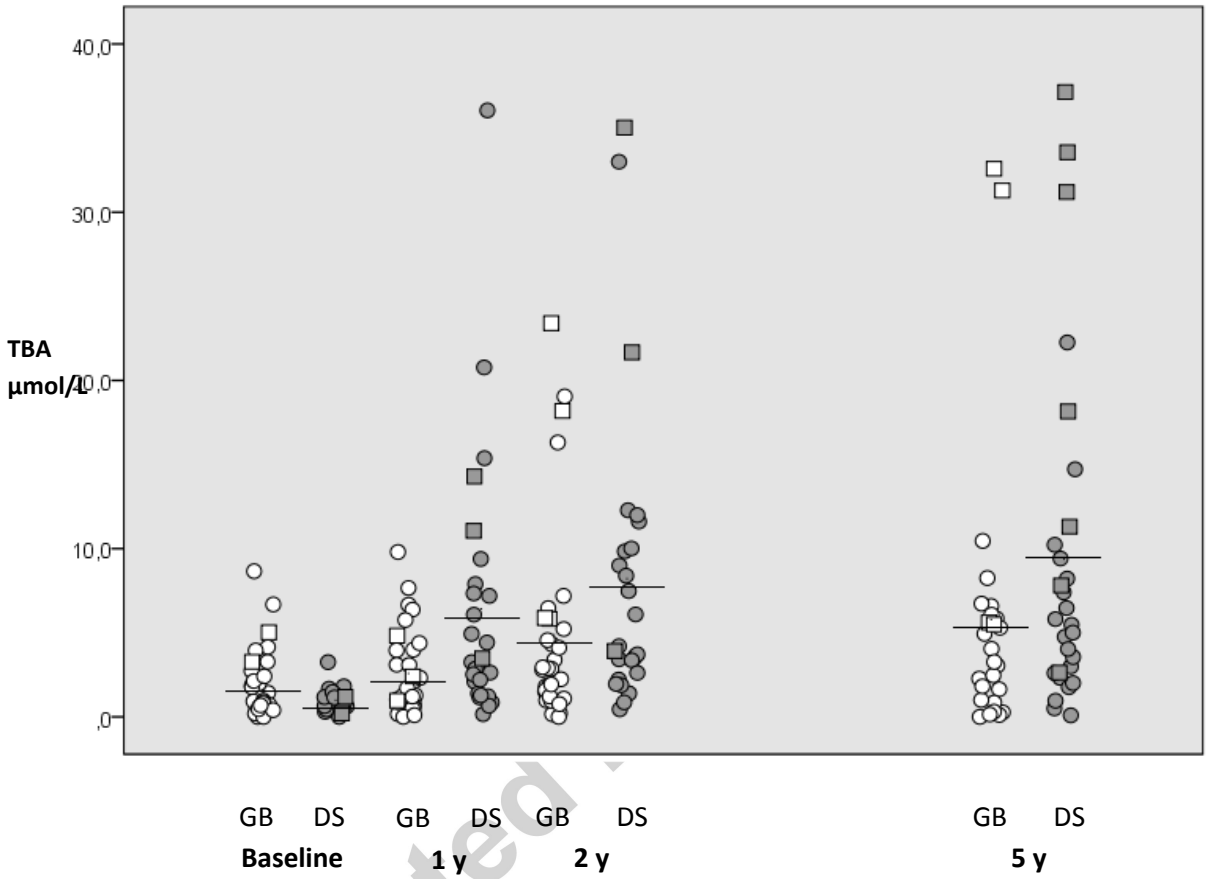
Figure 1. Total bile acid concentrations during 5 years of RYGB and BPD/DS



Abbreviations: RYGB, Roux-en-Y gastric bypass; BPD/DS, biliopancreatic diversion with duodenal switch; TBA, total bile acids; GB, gastric bypass; DS, duodenal switch.

Fasting serum concentrations of total bile acids from each individual measured up to 5 years after surgery. Circles represent patients with the gall bladder in situ, while squares represent patients with cholecystectomy. Horizontal black lines are observed mean values for the surgical group at each time point.

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